PATENT APPLICATION FORM (CONVENTION AND NON-CONVENTION)

10241/83

COMMONWEALTH OF AUSTRALIA

Regulation 9

Patents Act 1952

APPLICATION FOR A STANDARD PATENT OR A STANDARD PATENT OF ADDITION

We (a) BAYER AKTIENGESELLSCHAFT

of (b) Leverkusen, Germany

hereby apply for the grant of a (c) Standard Patent for an invention entitled (d) GROWTH-PROMOTING PHENYLETHYLAMINE DERIVATIVES

which is described in the accompanying (c) complete specification.

(e) For a Convention application — details of basic application(s) —

NUMBER	COUNTRY	DATE OF APPLICATION
P 32 34 995.5	GERMANY	22nd September 1982
P 33 06 159.9	GERMANY	22nd February 1983

(f)

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LODGED AT SUB-OFFICE 19 SEP 1983 Sydney

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I/W to Pt

Our address for service is ARTHUR S. CAVE & CO., Patent and Trade Mark Attorneys, 1 Alfred Street, Sydney, New South Wales, Australia 2000.

Dated this (i) 16th day of September, 1983.

BAYER AKTIENGESELLSCHAFT,
By Its Patent Attorneys,
(j) ARTHUR S. CAVE & CO.

(Signature)

JAMES G. SIELY. F.I.P.A.A.

To:

Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
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COMMONWEALTH OF AUSTRALIA

PATENTS ACT, 1952

COMPLETE SPECIFICATION

(ORIGINAL)

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TO BE COMPLETED BY APPLICANT

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Address for Service: ARTHUR S. CAVE & CO., Patent and Trade Mark Attorneys, 1 Alfred Street, Sydney, New South Wales, Australia, 2000.

Complete Specification for the invention entitled:

GROWTH-PROMOTING PHENYLETHYLAMINE DERIVATIVES

The following statement is a full description of this invention, including the best method of performing it known to me:-

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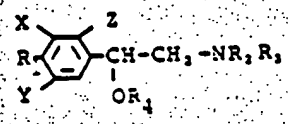
ASC 49

The invention relates to phenylethylamine derivatives and their use as growth-promoting additives in animal food.

The use of feedstuff additives to achieve higher increases in weight and improved feed utilisation is already widely practised in the nutrition of animals, especially in the fattening of pigs, cattle and poultry.

It has now been found that phenylethylamine derivatives of the general formula (I)



(I)

in which

X, Y and Z are identical or different and denote hydrogen, halogen, alkyl, alkoxy, alkenyl, hydroxyl, cyano or a COR' group, and

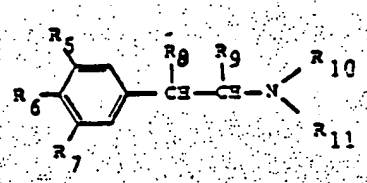
R_1 represents hydrogen, alkyl, halogen, hydroxyl, alkoxy, alkylthio, substituted or unsubstituted aryl, substituted or unsubstituted aryloxy or arylthio, or represents acyloxy or silyloxy, R' represents a hydroxyl-, alkoxy- or amino-group, and

R_2 and R_3 can be identical or different and represent hydrogen, straight-chain or branched C_1-C_8-alkyl, C_2-C_4-alkenyl and alkinyl, C_1-C_8-hydroxyalkyl, alkoxyalkyl, aminoalkyl, cycloalkyl or aralkyl radicals which are optionally substituted by halogen or phenyl, or represent an aliphatic or aromatic acyl radical or a silyl radical or substituted or unsubstituted aryl, examples of preferred substituents of the aryl radical being halogen, alkyl, alkoxy, halogenoalkyl, halogeno-

alkoxy and substituted or unsubstituted aryloxy or arylthio, or represent certain heterocyclic structures, such as imidazolinyl, thiazolinyl or pyrimidyl, or, together with the nitrogen atom, form an optionally substituted pyrimidine, piperidine, piperazine or morpholine radical or a saturated bicyclic radical, and

R_4 represents hydrogen, an aliphatic or aromatic acyl radical or a silyl radical,

and phenylethylamine derivatives of the general formula II



(II)

in which

R_5, R_6 and R_7 are identical or different and each represents hydrogen, hydroxyl, alkoxy or hydroxymethyl, and

R_8 denotes hydrogen or hydroxyl, and

R_9 represents hydrogen, straight-chain, branched or cyclic alkyl or alkenyl, aryl, acyl or aroyl, the alkyl, alkenyl and aryl radicals mentioned being optionally substituted by halogen, hydroxyl, alkyl, alkoxy, amino, optionally substituted phenyl or heteroaryl, and

R_{10} and R_{11} are identical or different and each represent hydrogen, straight-chain, branched or cyclic alkyl, alkenyl, aryl, acyl, aroyl, mono- or dialkylaminoalkyl, alkoxyalkyl, phenoxyalkyl or acylamino, the alkyl, alkenyl and aryl radicals mentioned being optionally substituted by halogen, amino, alkyl, alkoxy, hydroxyl, acylamino, optionally substituted phenyl or heteroaryl, or

R_{10} and R_{11}, together with the nitrogen atom, form

an optionally substituted pyrrolidine, piperidine, piperazine or morpholine radical,

and physiologically acceptable salts thereof, have an excellent growth-promoting action.

Preparation processes for compounds of this type are known, and are described, for example, in (a) A. Kleemann, Pharmazeutische Wirkstoffe: Synthesen, Patente, Anwendungen (Pharmaceutical Active Compounds: Syntheses, Patents, Uses); pages 35, 62, 169, 174, 175, 190, 196, 254, 296, 338, 346, 387, 389, 427, 438 and 461, G. Thieme, Stuttgart 1978; and in (b) O. Schier and A. Marxer in: Ullmanns Encyklopädie der technischen Chemie (Ullmann's Encyclopedia of Industrial Chemistry), Volume 12, pages 647-663, Verlag Chemie, Weinheim-New York 1976 (4th edition).

Where the compounds of the formula II are known, they are sympathicomimetic agents which directly or indirectly attack α- and/or β-adrenergic receptors. They show, in a known manner, marked actions on the circulation and vessels and actions on the respiratory tract. The actions are described in, for example, (a) G. Ehrhart and H. Ruschig, Arzneimittel (Medicaments), Volume 2, pages 133-165 and pages 257-269, Verlag Chemie, Weinheim 1972 (2nd edition); (b) G. Ehrhart and H. Ruschig, Arzneimittel (Medicaments), Volume 3, pages 63-68, Verlag Chemie, Weinheim 1972 (2nd edition); (c) E. Mutschler, Arzneimittelwirkungen (Medicament Actions), pages 242-265, Wissenschaftliche Verlagsgesellschaft, Stuttgart 1981 (4th edition) and (d) Progress in Medicinal Chemistry, Vol.6, pages 200-265, Editors: G.P. Ellis and G.B. West, Butterworths London 1969.

Preferred compounds of the formula I are phenylethylamine derivatives

in which

X, Y and Z can be identical or different and denote hydrogen, alkyl, halogen, hydroxyl or

alkoxy,

R_1 denotes hydrogen, hydroxyl, C_1-C_4-alkoxy or substituted or unsubstituted C_6-C_{10}-aryloxy or arylthio, and

R_2 and R_3 can be identical or different and represent hydrogen, lower alkyl radicals which are optionally substituted by halogen, hydroxyl or phenyl, or phenyl radicals which are optionally substituted by halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_6-C_{10}-aryloxy or arylthio, and

R_4 represents hydrogen.

Particularly preferred compounds are phenylethylamine derivatives of the formula (I),

in which

X, Y and Z can be identical or different and represent hydrogen or halogen,

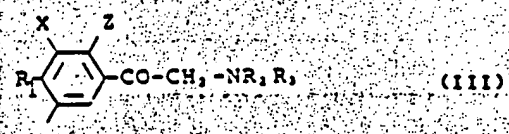
R_1 represents hydroxyl or C_1-C_4-alkoxy and

R_2 and R_3 can be identical or different and denote hydrogen, C_1-C_4-alkyl radicals, or phenyl which is substituted by optionally substituted C_6-C_{10}-aryloxy, and

R_4 denotes hydrogen.

The phenylethylamine derivatives used according to the invention, of the formula I, are not described in the literature, but can be prepared by known processes in which

a) compounds of the formula (III)



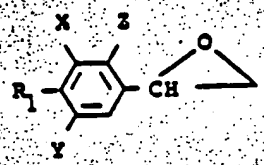
(III)

in which

X, Y, Z, R_1, R_2 and R_3 have the meaning given above,

are reduced, or in which

b) compounds of the formula (IV)



(IV)

in which

X, Y, Z and R_1 have the meaning given above,

are reacted with compounds of the formula (V)

(V)

in which

R_2 and R_3 have the meaning given above.

Compounds of the formula I, in which R_1 is acyloxy or silyloxy, and/or R_2 or R_3 and/or R_4 represent an aliphatic or aromatic acyl or silyl radical, are obtained by known methods from compounds of the general formula I, in which R denotes hydroxyl, and/or R_2 or R_3 and/or R_4 denote hydrogen, by reaction with suitable acylating or silylating agents.

The starting materials (III) and (IV) used here are either known or can be prepared by known preparation methods (see Lutz et al., J. Org. Chem. 12, 617-703, (1947); G.C. King and G.K. Ostrum, J. Org. Chem. 29, 3459 (1964)).

Phenylethylamine derivatives of the formula II which are preferred for the intended use according to the invention are those

in which

R_5, R_6 and R_7 are identical or different and each represent hydrogen, hydroxyl, hydroxymethyl or methoxy,

R_8 denotes hydrogen or hydroxyl,

R_9 represents hydrogen, straight-chain or branched alkyl or alkenyl groups having up to 5 carbon atoms, or phenyl or aralkyl having 7 to 10 carbon atoms, the aryl radicals mentioned being optionally substituted by chlorine, fluorine, lower alkyl having up to 4 carbon atoms, hydroxyl or alkoxy, and

R_{10} and R_{11} can be identical or different and represent hydrogen, straight-chain or branched alkyl having 1 to 8 carbon atoms, alkenyl having 2 to 4 carbon atoms, hydroxyalkyl, mono- and dialkylaminoalkyl and phenylalkylaminoalkyl, each having up to 4 carbon atoms in the alkyl radicals, or phenyl, aralkyl, methylenedioxyphenylalkyl or alkoxyalkyl radicals having 8 to 12 carbon atoms, or phenoxyalkyl radicals having 8 to 16 carbon atoms, it being possible for the alkyl groups mentioned to be optionally substituted by methyl or ethyl and for the phenyl radicals to be optionally substituted by halogen, in particular by chlorine or fluorine, hydroxyl, lower alkyl or lower alkoxy having up to 2 carbon atoms, or

R_{10} and R_{11}, together with the nitrogen atom, form an optionally substituted pyrrolidine, piperidine, piperazine or morpholine radical.

Compounds of the general formula II which are of very particular importance are those in which

R_5, R_6 and R_7 are identical or different and each represent hydrogen or hydroxyl, and

R_8 denotes hydroxyl, and

R_9 represents hydrogen or methyl, and

R_{10} and R_{11} are identical or different and each represent hydrogen, straight-chain or branched alkyl, each having up to 4 carbon atoms, it being possible for the alkyl groups to be optionally

substituted by phenyl, phenoxy, hydroxyphenyl or methylenedioxyphenyl,

The active compounds can be used as agents for promoting and accelerating growth and for improving feed utilisation in healthy and sick animals in all areas of animal husbandry.

The activity of the active compounds is largely independent of the species and sex of the animals. The active compounds prove particularly valuable in the rearing and keeping of young animals and fattening animals. The following stock animals and pets may be mentioned as examples of animals for which the active compounds can be used for promoting and accelerating growth and for improving feed utilisation: warm-blooded animals, such as cattle, pigs, horses, sheep, goats, cats, dogs and rabbits; fur-bearing animals, for example mink and chinchillas; poultry, for example chickens, geese, ducks, turkeys, pigeons, parrots and canaries, and cold-blooded animals, such as fish, for example carp, and reptiles, for example snakes.

The amount of the active compounds which is administered to the animals to achieve the desired effect can be varied substantially because of the advantageous properties of the active compounds. It is preferably about 0.01 to 50, in particular 0.1 to 10, mg/kg of body weight daily. The period of administration can be from a few hours or days up to several years. The appropriate amount of active compound and the appropriate period of administration depend, in particular, on the species, age, sex, state of health and nature of keeping and feeding of the animals, and can easily be determined by any expert.

The active compounds are administered to the animals by the customary methods. The nature of the administration depends, in particular, on the species, the behaviour and the state of health of the animals. Thus,

administration can be effected orally or parenterally, once or several times daily at regular or irregular intervals. For reasons of expediency, in most cases oral administration, in particular in the rhythm of the intake of food and/or drink by the animals, is to be preferred.

The active compounds can be administered as pure substances or in the formulated form, that is to say mixed with non-toxic inert carriers of any desired type, for example with carriers and in formulations such as are customary in the case of nutritive preparations.

The active compounds, in the formulated form, are optionally administered in a suitable form together with pharmaceutical active compounds, mineral salts, trace elements, vitamins, proteins, fats, colorants and/or flavouring agents.

Oral administration together with the feed and/or drinking water is recommended, the active compound being added to the total amount or only portions of the feed and/or drinking water as required.

The active compounds are added to the feed and/or drinking water by customary methods, by simple mixing as the pure substance mixture, preferably in the finely divided form or in the formulated form mixed with edible non-toxic carriers, optionally in the form of a premix or a feed concentrate.

The feed and/or drinking water can contain the active compounds in a concentration by weight of, for example, about 0.01 to 50 ppm, in particular 0.1 to 10 ppm. The optimum level of the concentration of the active compounds in the feed and/or drinking water depends, in particular, on the amount of feed and/or drinking water taken in by the animals and can easily be determined by any expert.

The nature of the feed and its composition is irrelevant. All the customary or specific feed compositions, which preferably contain the customary equilibrium

of energy substances and builder substances, including vitamins and mineral substances, necessary for balanced nutrition can be used. The feed can be composed of, for example, vegetable substances, for example hay, beet, cereals and cereal by-products, animal substances, for example meat, fats and bone meal, fish products, vitamins, for example vitamin A, D complex and B complex, proteins, aminoacids, for example DL methionine, and inorganic substances, for example lime and sodium chloride.

Feed concentrates contain the active compounds alongside edible substances, for example rye flour, maize flour, soya bean flour or lime, optionally with further nutrients and builder substances, as well as proteins, mineral salts and vitamins. They can be prepared by the customary mixing methods.

In premixes and feed concentrates, preferably, the active compounds can optionally also be protected from air, light and/or moisture by suitable agents which coat their surface, for example with non-toxic waxes or gelatine.

The following is an example of the composition of a feed for rearing chicks, which contains an active compound according to the invention: 200 g of wheat, 340 g of maize, 361 g of coarse soya bean meal, 60 g of beef tallow, 15 g of dicalcium phosphate, 10 g of calcium carbonate, 4 g of iodinated sodium chloride, 7.5 g of a vitamin/mineral mixture and 2.5 g of an active compound premix give, after careful mixing, 1 kg of feed.

One kg of feed mixture contains: 600 I.U. of vitamin A, 100 I.U. of vitamin D_3, 10 mg of vitamin E, 1 mg of vitamin K_3, 3 mg of riboflavin, 2 mg of pyridoxin, 20 mcg of vitamin B_{12}, 5 mg of calcium pantothenate, 30 mg of nicotinic acid, 200 mg of choline chloride, 200 mg of $MnSO_4 \times H_2O$, 140 mg of $ZnSO_4 \times 7H_2O$, 100 mg of $FeSO_4 \times 7H_2O$ and 20 mg of $CuSO_4 \times 5H_2O$.

The active compound premix contains the active

compounds in the desired amount, for example 10 mg, and also 1 g of DL-methionine as well as an amount of soya bean flour such that 2.5 g of premix are formed.

The following is an example of the composition of a feed for rearing pigs, which contains an active compound according to the invention: 630 g of shredded cereal feed (composed of 200 g of maize, 150 g of shredded barley, 150 g of shredded oats and 130 g of shredded wheat), 80 g of fish meal, 60 g of coarse soya bean meal, 60 g of tapioca meal, 38 g of brewer's yeast, 50 g of a vitamin/mineral mixture for pigs (composition, for example, as for the chick feed), 30 g of linseed cake meal, 30 g of maize gluten feed, 10 g of soya bean oil, 10 g of sugar cane molasses and 2 g of an active compound premix (composition, for example, as for the chick feed) give, after careful mixing, 1 kg of feed.

The feed mixtures indicated are intended preferably for rearing and fattening chicks or pigs respectively, but they can also be used, in the same or a similar composition, for rearing and fattening other animals.

Several feeding experiments and metabolic investigations have been carried out using the active compounds according to the invention. The active compounds used are those of Preparation Examples 1 and 2.

The following results were obtained:

Example 1

a) Animal characteristics and feed

a 1) rats, female	
a 2) number	18
a 3) breed	SPF Wistar, Hagemann breed
a 4) weight	90-150 g
a 5) condition	good
a 6) feed	
Raw nutrients*	
Raw protein	19.0
Raw fat	4.0

Raw fibres	6.0
Ash	7.0
Water	13.5
N-free extracted substances	50.5
Convertible energy:	
Kcal/kg	3,100
KJ/kg	13,000
Mineral nutrients*	
Calcium	0.9
Phosphorus	0.7
Magnesium	0.2
Sodium	0.2
Vitamins**	
Standard diet	
Vitamin A	15,000 IU
Vitamin D_3	600 IU
Vitamin E	75 mg
Vitamin K_3	3 mg
Vitamin B_1	18 mg
Vitamin B_2	12 mg
Vitamin B_6	9 mg
Vitamin B_{12}	24 mcg
Nicotinic acid	36 mg
Pantothenic acid	21 mg
Folic acid	2 mg
Biotin	60 mg
Choline	600 mg
Vitamin C	36 mg
Aminoacids*	
Lysine	0.9
Methionine + cystine	0.6
Phenylalanine + tyrosine	1.4
Arginine	1.1
Histidine	0.4
Tryptophan	0.2
Threonine	0.6

Isoleucine	0.9
Leucine	1.3
Valine	0.9
Trace elements**	
Manganese	75.0
Iron	135.0
Copper	13.0
Zinc	70.0
Iodine	0.9
Fluorine	9.0

*% in the diet (mean value)

**mg in 1 kg of diet (mean value)

b) Treatment of the animals

The rats were acclimatised to the new housing conditions for 2 days, the experimental feed without the addition of the active compound generally being administered. On the third day of the experiment, the animals were randomised and the experimental groups were then formed such that, between the groups, both the mean values and the scatters of the body weights were identical. A 5-day preliminary period was followed by an 8-day main period, in which feed intake, growth and feed utilisation were determined.

The following treatments were tested:

b 1) Negative control (n = 12)

b 2) 25 ppm (active compound from Preparation Example 1) (n = 6)

c) Result (feed intake, growth, feed utilisation) during the entire experimental period (13 days)

	Feed intake (g)	Growth (g)	Feed utilisation (g/g)
c 1) Negativ control	153	27.9	5.62
c 2) 25 ppm (active compound from Preparation Example 1)	175	43.7	4.03

Example 2

a) Animal characteristics and feed

a 1) rats, female

a 2) number 30

a 3) breed SPF Wistar, Hagemann breed

a 4) weight 90-150 g

a 5) condition good

a 6) feed as in Example 1

b) Treatment of the animals

The rats were acclimatised to the new housing conditions for 2 days, the experimental feed without the addition of the active compound generally being administered. On the third day of the experiment, the animals were randomised and the experimental groups were then formed such that, between the groups, both the mean values and the scatters of the body weights were identical. A 5-day preliminary period was followed by a 7-day main period, in which feed intake, growth and feed utilisation were determined.

The following treatments were tested:

b 1) Negative control (n = 24)

b 2) 0.2 ppm (active compound from Preparation Example 1)

c) Result (feed intake, growth, feed utilisation) during the entire experimental period (12 days)

	Feed intake (g)	Growth (g)	Feed utilisation (g/g)
c 1) Negative control	200	41.0	4.88
c 2) 0.2 ppm (active compound from Preparation Example 1)	213	50.5	4.21

Example 3

a) Animal characteristics and feed

a 1) rats, female	
a 2) number	18
a 3) breed	SPF Wistar, Hagemann breed
a 4) weight	90-150 g
a 5) condition	good
a 6) feed	as in Example 1

b) Treatment of the animals

The rats were acclimatised to the new housing conditions for 2 days, the experimental feed without the addition of the active compound generally being administered. On the third day of the experiment, the animals were randomised and the experimental groups were then formed such that, between the groups, both the mean values and the scatters of the body weights were identical. A 5-day preliminary period was followed by an 8-day main period, in which feed intake, growth and feed utilisation were determined.

The following treatments were tested:

b 1) Negative control (n = 12)

b 2) 25 ppm (active compound from Preparation Example 1) (n = 6)

c) Result (feed intake, growth, feed utilisation) during the entire experimental period (13 days)

	Feed intake (g)	Growth (g)	Feed utilisation (g/g)
c 1) Negative control	182	37.0	5.04
c 2) 25 ppm (active compound from Preparation Example 1)	187	42.4	4.41

Example 4

a) Animal characteristics and feed

a 1) rats, female

a 2) number 18

a 3) breed SPF Wistar, Hagemann breed

a 4) weight 90-150 g

a 5) condition good

a 6) feed as in Example 1

b) Treatment of the animals

The rats were acclimatised to the new housing conditions for 2 days, the experimental feed without the addition of the active compound generally being administered. On the third day of the experiment, the animals were randomised and the experimental groups were then formed such that, between the groups, both the mean values and the scatters of the body weights were identical. A 5-day preliminary period was followed by an 8-day main period, in which feed intake, growth and feed utilisation were determined.

The following treatments were tested:

b 1) Negative control (n = 12)

b 2) 25 ppm (active compound from Preparation Example 2) (n = 6)

c) Result (feed intake, growth, feed utilisation) during the entire experimental period (13 days)

	Feed intake (g)	Growth (g)	Feed utilisation (g/g)
c 1) Negative control	196	41.3	4.75
c 2) 25 ppm (active compound from Preparation Example 2)	199	45.1	4.41

Example 5

a) Animal characteristics and feed

a 1) rats, female
a 2) number — 18
a 3) breed — SPF Wistar, Hagemann breed
a 4) weight — 90-150 g
a 5) condition — good
a 6) feed — as in Example 1

b) Treatment of the animals

The rats were acclimatised to the new housing conditions for 2 days, the experimental feed without the addition of the active compound generally being administered. On the third day of the experiment, the animals were randomised and the experimental groups were then formed such that, between the groups, both the mean values and the scatters of the body weights were identical. A 5-day preliminary period was followed by an 8-day main period, in which feed intake, growth and feed utilisation were determined.

The following treatments were tested:

b 1) Negative control (n = 12)
b 2) 25 ppm (active compound from Preparation Example 2) (n = 6)

c) Result (feed intake, growth, feed utilisation) during the entire experimental period (13 days)

	Feed intake (g)	Growth (g)	Feed utilisation (g/g)
c 1) Negative control	152	27.9	5.62
c 2) 25 ppm (active compound from Preparation Example 2)	171	43.4	3.96

Example 6

a) Animal characteristics and feed

a 1) rats, female

a 2) number 18

a 3) breed SPF Wistar, Hagemann breed

a 4) weight 90-150 g

a 5) condition good

a 6) feed as in Example 1

b) Treatment of the animals

The rats were acclimatised to the new housing conditions for 2 days, the experimental feed without the addition of the active compound generally being administered. On the third day of the experiment, the animals were randomised and the experimental groups were then formed such that, between the groups, both the mean values and the scatters of the body weights were identical. A 5-day preliminary period was followed by an 8-day main period, in which feed intake, growth and feed utilisation were determined.

The following treatments were tested:

b 1) Negative control (n = 12)

b 2) 25 ppm (active compound from Preparation Example 2) (n = 6)

c) Result (feed intake, growth, feed utilisation) during the entire experimental period (13 days)

	Feed intake (g)	Growth (g)	Feed utilisation (g/g)
c 1) Negative control	182	37.0	5.04
c 2) 25 ppm (active compound from Preparation Example 2)	183	43.2	4.36

Example 7 - Rats

a. Description of the experiment

Before the start of the feeding experiment, the rats were acclimatised to the new housing conditions for two days, the experimental feed without the addition of the active compound generally being administered. On the third day of the experiment, the animals were randomised and the experimental groups were then formed such that, between the groups, both the mean values and the scatters of the body weights were identical.

The feeding experiment, in which the feed intake, the increase in body weight and the feed utilisation were determined individually, lasted for 15 days.

The active compounds mixed with the feed were: 1-(3,4-dihydroxyphenyl)-2-[1-methyl-2-(3,4-methylenedioxyphenyl)ethylamino]ethanol hydrochloride (= compound I), 2-amino-1-(3-hydroxyphenyl)ethanol hydrochloride (= compound II), 2-amino-1-(3-hydroxyphenyl)propanol hydrogen tartrate (= compound III), 1-(4-hydroxyphenyl)-2-(1-methyl-3-phenylpropylamino)-propanol hydrochloride (= compound IV), 2-ethylamino-1-(3-hydroxyphenyl)-ethanol hydrochloride (= compound V), 1-(3,5-dihydroxyphenyl)-2-(3-phenylpropylamino)propanol as the 4-aminobenzoic acid salt (= compound VI) and 1-(3-hydroxyphenyl)-2-(1,1-dimethyl-2-phenylethylamino)-ethanol as the 4-aminobenzoic acid salt (= compound VII).

5-/2-/(1,1-dimethylethyl)amino7-1-hydroxyethyl7-2-hydroxybenzamid . HCl (= compound VIII)

The results are shown in a summarising table.

b. Animal characteristics and feed

Rats, female, SPF-Wistar

36 animals/experiment

Weight: 90 to 150 g

Feed: Maintenance diet for rats having the following composition:

Raw nutrients*		Vitamins**	
Raw protein	19.0	Standard diet	
Raw fat	4.0	Vitamin A	15,000 IU
Raw fibre	6.0	Vitamin D	1,600 IU
Ash	7.0	Vitamin E	75 mg
Water	13.5	Vitamin K	3 mg
N-free extracted substances		Vitamin B_1	18 mg
	50.5	Vitamin B_2	12 mg
Convertible energy:		Vitamin B_6	9 mg
Kcal/kg	3,100	Vitamin B_{12}	24 mcg
KJ/kg	13,000	Nicotinic acid	36 mg
Mineral nutrients*		Pantothenic acid	21 mg
Calcium	0.9	Folic acid	2 mg
Phosphorus	0.7	Biotin	60 mcg
Magnesium	0.2	Choline	600 mg
Sodium	0.2	Vitamin C	36 mg
Trace elements**		Aminoacids**	
Manganese	75.0	Lysine	0.9
Iron	135.0	Methionine + cystine	0.6
Copper	13.0	Phenylalanine + tyrosine	1.4
Zinc	70.0	Arginine	1.1
Iodine	0.9	Histidine	0.4
Fluorine	9.0	Tryptophan	0.2
		Threonine	0.6
		Isoleucine	0.9
		Leucine	1.3
		Valine	0.9

*in the diet (mean value)

**mg in 1 kg of diet (mean value)

Example 8 - Broilers

a. Description of the experiment

The animals, which were kept in cages, were used in the experiment, which lasted for a total period of 14 days, when they were aged from 3 to 5 days.

During the experimental period, the animals received feed to which the claimed compounds 1-(3,4-dihydroxyphenyl)-2-[1-methyl-2-(3,4-methylenedioxyphenyl)-ethylamino]ethanol hydrochloride (= compound I), 2-amino-1-(3-hydroxyphenyl)ethanol hydrochloride (= compound II), 2-amino-1-(3-hydroxyphenyl)propanol hydrogen tartrate (= compound III), 1-(4-hydroxyphenyl)-2-(1-methyl-3-phenyl-propylamino)-propanol hydrochloride (compound IV), 2-ethylamino-1-(3-hydroxyphenyl)ethanol hydrochloride (= compound V), 1-(3,5-dihydroxyphenyl-2-(3-phenylpropyl-amino)propanol as the 4-aminobenzoic acid salt (= compound VI) and 1-(3-hydroxyphenyl)-2-(1,1-dimethyl-2-phenyl-ethylamino)-ethanol as the 4-aminobenzoic acid salt (= compound VII) had been admixed in a dose of 5 or 25 ppm. A negative control (non-supplemented feed) was also run. At the start of the experiment, all the animals in each experimental group had the same starting weight.

The rates of increase in growth, the feed consumption and the feed utilisation were used as evaluation criteria.

The results are shown in a table.

b. Animal characteristics and feed

Assorted fattening hybrids, male

24 animals/experiment (4 x 6)

Weight 50 to 65 g

Feed: Höveler Kükenalleinfutter KA 57 without the addition of antibiotics and coccidiostatic agents and having the following composition:

Value-determining constituents:

18 % of raw protein
7 % of raw fibre
8 % of ash
1 % of calcium
0.7% of phosphorus

Composition:

54 % of shredded cereal feed (40% of maize, 12% of wheat)

17.5% of coarse soya bean meal
5.2% of maize gluten feed
5.2% of whole wheat meal
3.1% of fish meal
3.1% of tapioca meal
3.1% of lucerne green meal
2.1% of wheatgerm (ground)
1.7% of meat-and-bone meal
1.6% of milk powder
1.4% of limestone
1.0% of calcium phosphate
1.0% of molasses

Results (growth, feed intake, feed utilisation)

a. Rats

Substance	ppm	Additional growth	Feed intake	Feed utilisation
Control	--	100%	100%	100%
Compound I	25	112%	104%	92.9%
Compound III	25	107%	98%	91.6%
Compound III	25	103%	99%	96.1%
Compound IV	25	105%	101.7%	96.9%
Compound V	25	115%	104%	90.4%
Compound VIII	25	125%	106%	84,8%

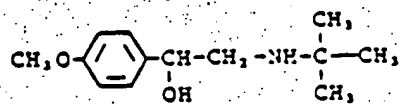
b. Chicks

Substance	ppm	Additional growth	Feed intake	Feed utilisation
Control	--	100%	100%	100%
Compound VI	5	101.8%	96.2%	94.4%
Compound V	5	102.0%	99.0%	97.5%
Compound VII	25	102.0%	100.0%	98.1%
Compound II	25	105.0%	103.3%	98.8%

Preparation Examples

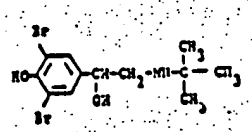
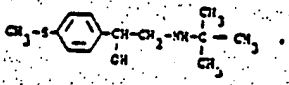
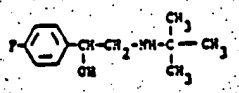
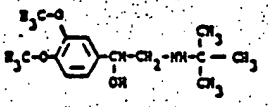
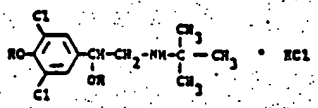
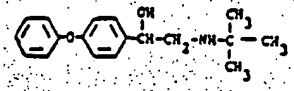
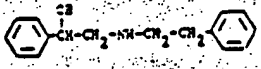
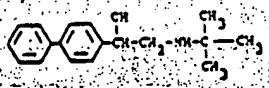
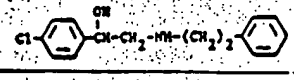
Example 1

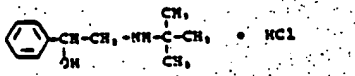
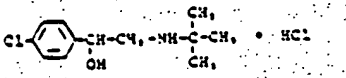
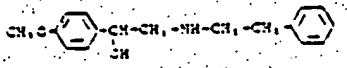
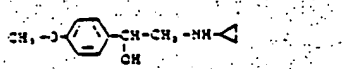
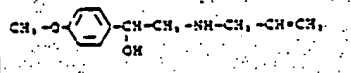
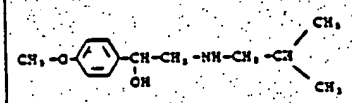
2-t-Butylamino-1-(4-methoxyphenyl)-ethanol



24.1 g (92.2 mmol) of ω-tert.-butylamino-4-methoxy-acetophenone hydrochloride are dissolved in 125 ml of methanol and 80 ml of water, and a solution of 4.25 g (112 mmol) of sodium borohydride in 8.5 ml of water is added dropwise, the solution being kept at between pH 3 and pH 7 by simultaneous addition of approx. 15% strength hydrochloric acid. The mixture is stirred for a further 30 minutes, the pH is brought to 1 with hydrochloric acid and the mixture is filtered. The mixture is rendered alkali with concentrated ammonia solution, and the precipitated product is filtered off under suction, washed with water and dried. 15 g of colourless crystals of melting point 104°C are obtained.

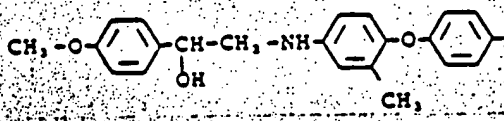
The following compounds were prepared analogously:

Example No.	Structural formula	Melting point °C
2		130
3		240
4		96
5		107
6		218
7		252
	$^1/_2$ naphthalene-1,5-disulphonic acid	
8		225
9		139
10		208

Example No.	Structural formula	Melting point °C
11		219-220
12		195-197
13		107-109
14		75-76
15		82-83
16		82-83

Example 17

1-(4-Methoxyphenyl)-2-[3-methyl-4-(4-trifluoromethylthiophenoxy)-phenylamino]-ethanol 1/2 naphthalenedisulphonate

 1/2 $C_{10}H_8O_6S_2$

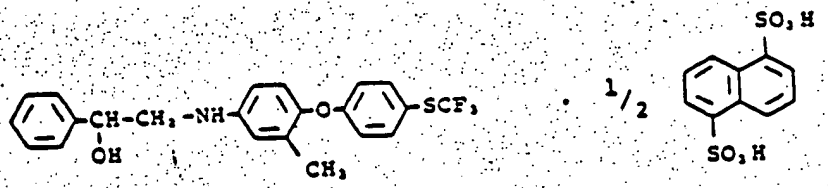
3.1 g of 4-methoxy-ω-[3-methyl-4-(4-trifluoromethylthiophenyl)-phenylamino]-acetophenone are dissolved in a mixture of 20 ml of absolute tetrahydrofuran and 100 ml of methanol, and 0.3 g of sodium borohydride is added, while stirring. The mixture is stirred for 1 hour, rendered acidic with 1 N hydrochloric acid and evaporated

down. The residue from evaporation is taken up with ethyl acetate/sodium bicarbonate solution, and the phases are separated. The ethyl acetate phase is washed twice with water, dried and evaporated down. Since the product does not crystallise, the naphthalene-1,5-disulphonate is prepared. 3.4 g of the salt, of melting point 266-269°C, are obtained.

The following compounds were obtained analogously:

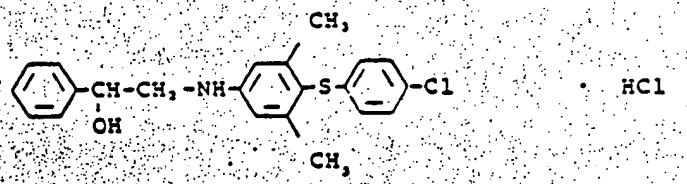
Example 18

1-Phenyl-2-[3-methyl-4-(4-trifluoromethylthio-phenoxy)-phenylamino]-ethanol, crystallised with 1/2 naphthalene-1,5-disulphonic acid, melting point 210°C



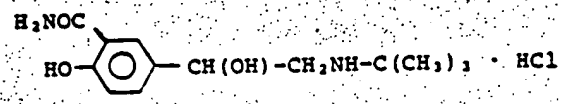
Example 19

2-[4-(4-Chlorophenylthio)-3,5-dimethyl-phenylamino]-1-phenylethanol hydrochloride of melting point 175-180°C (decomposition)



Example 20

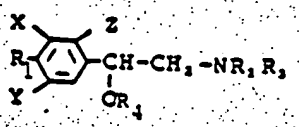
5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxy-benzamide · HCl



6.0 g 5-[2-[N-(1,1-dimethylethyl)— benzyl-amino]acetyl]-2-hydroxy-benzamide · HCl are disolved in a mixture of 120 ml methanol and 90 ml water, 1.5 g Pd/C (10%) is added and the suspension is hydrogenated at roomtemperature and normal pressure. The catalyst is removed and the solution is concentrated. The residue is recrystallised from methanol/ isopropyl acetate.
m.p. 205°.

The claims defining the invention are as follows:-

1) Phenylethylamine derivatives of the general formula (I)



(I)

in which

X, Y and Z are identical or different and denote hydrogen, halogen, alkyl, alkoxy, alkenyl, hydroxyl, cyano or a group, and

R_1 represents hydrogen, alkyl, halogen, hydroxyl, alkoxy, alkylthio, substituted or unsubstituted aryl, substituted or unsubstituted aryloxy or arylthio, or represents acyloxy or silyloxy, R' represents a hydroxyl-, alkoxy- or amino-group, and

R_2 and R_3 can be identical or different and represent hydrogen, straight-chain or branched C_1-C_8-alkyl, C_2-C_4-alkenyl and alkinyl, C_1-C_8-hydroxyalkyl, alkoxyalkyl, aminoalkyl, cycloalkyl or aralkyl radicals which are optionally substituted by halogen or phenyl, or represent an aliphatic or aromatic acyl radical or a silyl radical or substituted or unsubstituted aryl, examples of preferred substituents of the aryl radical being halogen, alkyl, alkoxy, halogenoalkyl, halogenoalkoxy and substituted or unsubstituted aryloxy or arylthio, or represent certain heterocyclic structures, such as imidazolinyl, thiazolinyl or pyrimidyl, or, together with the nitrogen atom, form an optionally substituted pyrimidine, piperidine, piperazine or morpholine radical or a saturated bicyclic radical, and

R_4 represents hydrogen, an aliphatic or aromatic acyl radical or a silyl radical,

and their physiologically acceptable salts.

2) Phenylethylamine derivatives according to Claim 1, in which

X, Y and Z can be identical or different and denote hydrogen, halogen, alkyl, hydroxyl or alkoxy,

R_1 denotes hydrogen, hydroxyl, C_1-C_4-alkoxy or substituted or unsubstituted C_6-C_{10}-aryloxy or arylthio, and

R_2 and R_3 can be identical or different and represent hydrogen, lower alkyl radicals which are optionally substituted by halogen, hydroxyl or phenyl, or phenyl radicals which are optionally substituted by halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_6-C_{10}-aryloxy or arylthio, and

R_4 represents hydrogen.

3) Phenylethylamine derivatives according to Claim 1, in which

X, Y and Z can be identical or different and represent hydrogen or halogen,

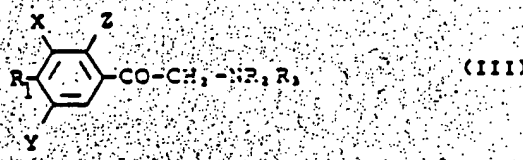
R_1 represents hydroxyl or C_1-C_4-alkoxy and

R_2 and R_3 can be identical or different and denote hydrogen, C_1-C_4-alkyl radicals, or phenyl which is substituted by optionally substituted C_6-C_{10}-aryloxy, and

R_4 denotes hydrogen.

4) Process for the preparation of phenylethylamine derivatives of the formula (I) according to Claim 1, characterised in that

a) compounds of the formula (III)



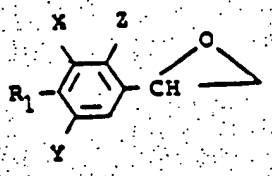
(III)

in which

X, Y, Z, R_1, R_2 and R_3 have the meaning given above,

are reduced, or

b) compounds of the formula (IV)



(IV)

in which

X, Y, Z and R_1 have the meaning given above,

are reacted with compounds of the formula (V)

(V)

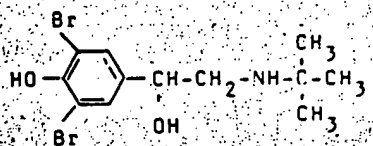
in which

R_2 and R_3 have the meaning given above,

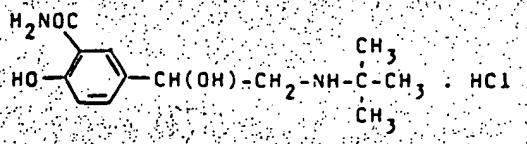
or, for the preparation of compounds of the formula I, in which R_1 is acyloxy or silyloxy, and/or R_2 or R_3 and/or R_4 represent an aliphatic or aromatic acyl or silyl radical,

c) compounds of the general formula I, in which R_1 denotes hydroxyl, and/or R_2 or R_3 and/or R_4 denote hydrogen, are acylated or silylated with suitable agents by known methods.

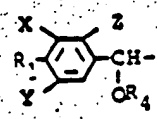
5) The compound of formula



6) The compound of formula



7) Use of phenylethylamine derivatives of the general formula (I)



(I)

in which

X, Y and Z are identical or different and denote hydrogen, halogen, alkyl, alkoxy, alkenyl, hydroxyl, cyano or a COR' group, and

R_1 represents hydrogen, alkyl, halogen, hydroxyl, alkoxy, alkylthio, substituted or unsubstituted aryl, substituted or unsubstituted aryloxy or arylthio, or represents acyloxy or silyloxy, R' represents a hydroxyl-, alkoxy- or amino-group, and

R_2 and R_3 can be identical or different and represent hydrogen, straight-chain or branched C_1-C_8-alkyl, C_2-C_4-alkenyl and alkinyl, C_1-C_8-hydroxyalkyl, alkoxyalkyl, aminoalkyl, cycloalkyl or aralkyl radicals which are optionally substituted by halogen or phenyl, or represent an aliphatic or aromatic acyl radical or a silyl radical or substituted or unsubstituted aryl, examples of preferred substituents of the aryl radical being halogen, alkyl, alkoxy, halogenalkyl, halogenoalkoxy and substituted or unsubstituted aryloxy or arylthio, or represent certain heterocyclic structures, such as imidazolinyl, thiazolinyl or pyrimidyl, or, together with the nitrogen atom, form an optionally substituted pyrimidine, piperidine, piperazine or morpholine radical or a saturated bicyclic radical, and

R_4 represents hydrogen, an aliphatic or aromatic acyl radical or a silyl radical,

and their physiologically acceptable salts as growth-promoters for animals.

8). Use of phenylethylamine derivatives of the formula

(I)

in which

X, Y and Z can be identical or different and denote hydrogen, halogen, alkyl, hydroxyl or alkoxy,

R_1 denotes hydrogen, hydroxyl, C_1-C_4-alkoxy or substituted or unsubstituted C_6-C_{10}-aryloxy or arylthio, and

R_2 and R_3 can be identical or different and represent hydrogen, lower alkyl radicals which are optionally substituted by halogen, hydroxyl or phenyl, or phenyl radicals which are optionally substituted by halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_6-C_{10}-aryloxy or arylthio, and

R_4 represents hydrogen,

as growth-promoters for animals.

9) Use of phenylethylamine derivatives of the formula (I)

in which

X, Y and Z can be identical or different and represent hydrogen or halogen,

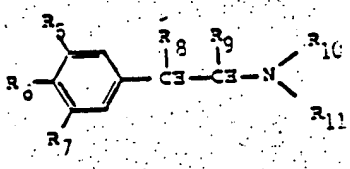
R_1 represents hydroxyl or C_1-C_4-alkoxy and

R_2 and R_3 can be identical or different and denote hydrogen, C_1-C_4-alkyl radicals, or phenyl which is substituted by optionally substituted C_6-C_{10}-aryloxy, and

R_4 denotes hydrogen,

as growth-promoters for animals.

10) Use of phenylethylamine derivatives of the general formula II



(II)

in which

R_5, R_6 and R_7 are identical or different and each represents hydrogen, hydroxyl, alkoxy or hydroxymethyl, and

R_8 denotes hydrogen or hydroxyl, and

R_9 represents hydrogen, straight-chain, branched or cyclic alkyl or alkenyl, aryl, acyl or aroyl, the alkyl, alkenyl and aryl radicals mentioned being optionally substituted by halogen, hydroxyl,

alkyl, alkoxy, amino, optionally substituted phenyl or heteroaryl, and

R_{10} and R_{11} are identical or different and each represent hydrogen, straight-chain, branched or cyclic alkyl, alkenyl, aryl, acyl, aroyl, mono- or dialkylaminoalkyl, alkoxyalkyl, phenoxyalkyl or acylamino, the alkyl, alkenyl and aryl radicals mentioned being optionally substituted by halogen, amino, alkyl, alkoxy, hydroxyl, acylamino, optionally substituted phenyl or heteroaryl, or

R_{10} and R_{11}, together with the nitrogen atom, form an optionally substituted pyrrolidine, piperidine, piperazine or morpholine radical,

and their physiologically acceptable salts as growth-promoters for animals.

11) Use of phenylethylamine derivatives of the general formula II according to Claim 10,

in which

R_5, R_6 and R_7 are identical or different and each represent hydrogen, hydroxyl, hydroxymethyl or methoxy,

R_8 denotes hydrogen or hydroxyl,

R_9 represents hydrogen, straight-chain or branched alkyl or alkenyl groups having up to 5 carbon atoms, or phenyl or aralkyl having 7 to 10 carbon atoms, the aryl radicals mentioned being optionally substituted by chlorine, fluorine, lower alkyl having up to 4 carbon atoms, hydroxyl or alkoxy, and

R_{10} and R_{11} can be identical or different and represent hydrogen, straight-chain or branched alkyl having 1 to 8 carbon atoms, alkenyl having 2 to 4 carbon atoms, hydroxyalkyl, mono- and dialkylaminoalkyl and phenylalkylaminoalkyl, each having up to 4 carbon atoms in the alkyl radicals, or phenyl, aralkyl, methylenedioxyphenylalkyl or

alkoxyalkyl radicals having 8 to 12 carbon atoms, or phenoxyalkyl radicals having 8 to 16 carbon atoms, it being possible for the alkyl groups mentioned to be optionally substituted by methyl or ethyl and for the phenyl radicals to be optionally substituted by halogen, in particular by chlorine or fluorine, hydroxyl, lower alkyl or lower alkoxy having up to 2 carbon atoms, or

R_{10} and R_{11}, together with the nitrogen atom, form an optionally substituted pyrrolidine, piperidine, piperazine or morpholine radical,

as growth-promoters for animals.

12) Use of phenylethylamine derivatives of the general formula II according to Claim 10,

in which

R_5, R_6 and R_7 are identical or different and each represent hydrogen or hydroxyl, and

R_8 denotes hydroxyl, and

R_9 represents hydrogen or methyl, and

R_{10} and R_{11} are identical or different and each represent hydrogen, straight-chain or branched alkyl, each having up to 4 carbon atoms, it being possible for the alkyl groups to be optionally substituted by phenyl, phenoxy, hydroxyphenyl or methylenedioxyphenyl,

as growth-promoters for animals.

13) Use of phenylethylamine derivatives of the general formulae (I) or (II) of Claims 1 and 10 respectively, as a growth-promoting additive in animal feed.

14) Use of phenylethylamine derivatives of the general formulae (I) or (II) of Claims 1 and 10 respectively according to one or more of Claims 1 to 3, in amounts of from 0.01 to 50 mg per kg of body weight daily, as growth promoters.

15) Animal feed containing phenylethylamine derivatives of the general formulae (I) or (II) of Claims 1 and 10

respectively.

16) Growth-promoting agent for animals, consisting of phenylethylamine derivatives of the general formulae (I) or (II) of Claims 1 and 10 respectively.

17) Growth-promoting agent for animals, containing phenylethylamine derivatives of the general formulae (I) or (II) of Claims 1 and 10 respectively.

18) Process for the preparation of growth-promoting animal feed, characterised in that phenylethylamine derivatives of the general formulae (I) or (II) of Claims 1 and 10 respectively are added to the animal feed.

19) Premixes for the nutrition of animals, containing phenylethylamine derivatives of the general formulae (I) or (II) of Claims 1 and 10 respectively.

DATED this 16th day of September, 1983.

BAYER AKTIENGESELLSCHAFT,
By Its Patent Attorneys,
ARTHUR S. CAVE & CO.

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